Original Article

Enzyme Based Glucose Biosensor- An Overview

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Abstract

Nanotechnology has affected almost all aspects of biomedicine. The integration of nanomaterials has contributed to the selectivity, the versatility, the stability and especially the sensitivity of bioelectronic devices, including biosensors. In this field, nanomaterials have been employed as enzyme immobilizers, enzyme stabilizers, surface modifiers or labeling factors or have provided individualized catalytic effects. Among other sensing platforms, glucose biosensors are of special clinical and industrial significance because of their role in monitoring blood-glucose levels in diabetes mellitus, one of the most prevalent metabolic disorders worldwide. Similar to other sensing platforms, glucose biosensors have been the target to incorporate nanomaterials, including metal nanoparticles (MNPs). MNPs possess a number of general inherent characteristics including large surface-to-volume ratio, good electrocatalytic activity and high chemical reactivity. Furthermore, MNPs help to immobilize glucose oxidase on the surface of enzyme-based glucose biosensors.

Keywords: Biosensor, Blood-glucose level, Diabetes mellitus, Electrochemical biosensor, Enzyme, Enzyme-based glucose biosensor, Glucose, Glucose oxidase (GOx), Metal nanoparticle (MNP).

INTRODUCTION

A biosensor is a small analytical instrument that uses a recognition element connected to a transducer to identify and measure a particular molecular entity (analyte) (reader). Numerous investigations have concentrated on developing brand-new biosensor assembly, immobilisation techniques, and applications of cutting-edge materials that can bring these techniques to life [1-3]. A reliable biosensor must offer a quick, inert, stable, inexpensive platform for the selective, accurate detection of a target molecule [2,4]. Numerous potential uses for biosensors include food analysis, bioprocess monitoring, environmental monitoring, clinical diagnosis and prognosis, and bioassays [5]. Since there are numerous clinical and experimental uses for glucose sensing, the development of quick, accurate, and affordable biosensors is an appealing research area in numerous labs all over the world. In fact, glucose biosensors are one of the few sensing products that have been commercially successful to date [6].

Long ago, commercial strips for self-monitoring blood glucose were introduced; Wang provided a good history of these strips [7]. Glucose biosensors can detect glucose either directly or by encouraging its conversion to other measurable electroactive molecules. For the determination of glucose, both enzyme-

based and enzyme-independent methods have been used up to this point. But it appears that immobilised glucose oxidase (GOx)-based detection is the most common. New immobilisation techniques, electrode-surface modifications, and immobiliser chemicals are always requested because enzyme immobilisation unquestionably impacts the biosensor's response [8]. The selection of surface modifiers and immobilisers is critical in enzyme-based biosensing for increasing not only the sensitivity but also the stability of the device because a good modifier or immobiliser can stop enzyme leakage, maintain enzyme bioactivity, and extend the shelf life of the biosensor.

In enzyme-based biosensors, a number of substances, including polymers, porous alumina, clay, phospholipid bilayer, and zeolite, have been utilised as immobilisers. The goal of current research is to incorporate nanomaterials into the design of biosensors to increase their stability, sensitivity, and detection accuracy. By introducing innovative nanomaterials throughout the past ten years, such as nanotubes (NTs), quantum dots, nanosilica, nanofibers, nanoparticles (NPs), and nanorods, nanotechnology has opened up intriguing new possibilities for biosensors [9].
Nanomaterials are suited for incorporation into novel minidevices, microdevices, and nanodevices because they have a number of significant intrinsic benefits over conventional materials. Large surface-to-volume ratios, incredibly small sizes, distinct behaviour, high chemical reactivity, and customizable properties are a few of these characteristics [10]. Nanoscale materials are attractive prospects for biotechnology and bioanalytical chemistry because of their unique properties.

Metal nanoparticles (MNPs) have a wide range of uses in the biological sciences. By increasing surface area and aiding in the flow of electrons from enzyme to electrode, MNPs have recently found widespread use in glucose biosensors, which has improved detection signal. Additionally, the assembly of the NPs attached to GOx on the electrode surface is made easier by the magnetic properties of MNPs [11]. On the electrode surface, they can also create conductive wires [12]. Biosensors have generally become smaller as a result of the incorporation of nanomaterials. Numerous Metal Nano Particles (MNPs), such as Au, Pt, Ag, Fe, Zn, Cu, Pd, Ir, and alloys, have been used as immobilisers, labelling agents, or modification agents in glucose biosensors [13–15]. In this article, we examine the most recent developments in MNP-based enzyme-based and enzyme-independent glucose biosensors.

Diabetes mellitus is a major contributor to heart disease, renal failure, and blindness, making it one of the leading causes of mortality and disability worldwide. In the entire world, 200 million people have diabetes mellitus. By 2030, this number is projected to reach more than 300 million [16]. For the confirmation of effective treatment, regular physiological blood glucose measurement is essential to prevent diabetic emergencies [17–20]. Therefore, for many years, both the medical and food businesses have been interested in the creation of highly sensitive, affordable, trustworthy glucose sensors with outstanding selectivity [21–22]. Over the past forty years, glucose sensor research and development, as well as the industry, have been dominated by glucose oxidase (GOx)-based glucose biosensors.

This is because sensitive and trustworthy blood glucose monitoring is highly demanded in biological and clinical aspects [23–26]. Enzyme-based glucose determination still has several drawbacks. Examples include challenging enzyme immobilisation, essential operational parameters such ideal temperature and pH, chemical instability, and high cost [27–28]. To address these issues, a lot of emphasis has been dedicated to the development of nonenzymatic electrodes. The creation of nonenzymatic glucose sensors has been thoroughly studied by numerous researchers. These electrodes' shortcomings, such as inadequate selectivity, high cost, or chloride ion poisoning, severely restrict the range of applications for which they can be used. Therefore, the creation of a nonenzymatic glucose sensor that is inexpensive, highly selective, quick, and reliable is still urgently needed.

Numerous new materials and devices with desirable features have been made possible by recent advances in nanotechnology. These products serve a variety of electrochemical sensor and biosensor applications [28–32]. In essence, even without altering the materials' chemical composition, it is feasible to modify the fundamental properties of materials by constructing nanostructures. This has led to the emergence in the field of nanotechnology of an appealing universe of low dimensional systems as well as the current trends on the manufacture of useful nanostructured arrays. Additionally, the utilisation of nanostructures in optical excitations and the efficient transit of electrons make them crucial to the operation and integration of nanoscale devices [33–35]. In actuality, nanosystems are the smallest three-dimensional structures that can be used for effective electron transport and, consequently, for effective development of biosensors.

2. Enzyme-based glucose biosensors

The most straightforward, trustworthy, and industrially viable glucose detection technique has been found to be GOx-based [36]. GOx should initially be immobilised onto a surface in order to sense glucose. The oxidation of glucose to gluconolactone and hydrogen peroxide is catalysed by GOx. Two protons and two electrons are transferred from glucose to the flavine moiety of GOx during this reaction, and the signal that results from this reaction is detected using a reading device [37–38].

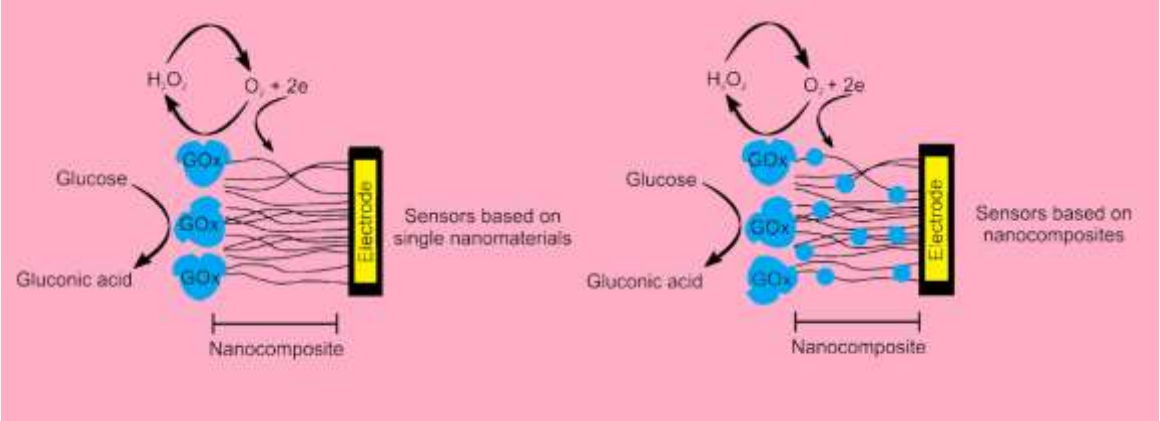

Fig. 1 shows the concept and workings of glucose sensors made from single nanomaterials and nanocomposites.

We examine new biosensors that incorporate various MNPs in their architectures in the following subsections. We also go over the overall characteristics of various MNPs and the numerous functions that they serve in various biosensors.

2.1. Au Nano Particles used in enzyme based glucose biosensor:

Au-NPs have several uses in electron microscopy as contrast agents, biology, electronics, and nanotechnology because of their distinctive optical and electrical features [39]. Since they exhibit electrocatalytic activity, Au-NPs have also been widely employed in glucose biosensors as immobiliser agents and electrode modifiers [41]. The most stable MNPs are Au-NPs [40]. In addition, AuNPs have the ability to bind to a variety of biological entities, including nucleic acids, super antigens, and antibodies [42–43]. AuNPs also have the typical characteristics of other nanomaterials (e.g., larger surface-to-volume ratio, which is important for increasing the loading capacity of GOx).

An effective substrate for binding the GOx enzyme must be provided by a surface modification while maintaining the electrode's original characteristics. Au-NPs have a remarkable affinity for GOx when they are decorated on the electrode surface. Several biosensors currently use this characteristic to increase the amount of enzyme immobilised. The deposition of GOx is more manageable on such surface-modified

electrodes, which is another feature. Nanomaterials also shield the enzyme from deterioration and stop its leaking.

In AuNP-based glucose biosensors, composites or films and polymers (such chitosan and mesoporous silica) have been employed to improve surface stability, stop enzyme leakage, and shield it from extremely harsh circumstances [44–46]. In order to create enzyme-based glucose sensors, other modifiers have also been used, such as a self-assembling double-layer 2-dimensional network of (3-mercaptopropyl)-trimethoxysilane and AuNPs [47], a composite of AuNPs and conductive polyaniline nanofibers [48], and a novel multilayer AuNP/MWCNT/GOx membrane [49].

German et al. [50] recently researched and compared various glucose biosensors based on GOx immobilised on bare carbon rod electrodes modified with AuNPs to biosensors based on GOx immobilised on bare carbon rod electrodes. To extend the linear detection range of biosensors, they used pyrrole enzymatic polymerization. In their investigation, the limit of detection (LOD) for glucose was 0.07 mmol/L. They demonstrated how the sizes of AuNPs affected the sensitivity of analytical systems modified with polypyrrole. Higher amperometric responses were attained with smaller AuNPs at the same glucose concentration both before and after the polypyrrole layer was formed [50]. Some of the manufactured biosensors have been effectively used to measure the levels of glucose in samples of human blood and urine [56]. AuNPs decreased the response time to the analyte glucose and enhanced calibration sensitivity and stability of the sensors in the majority of reported investigations. AuNPs were created in-situ on an eggshell membrane that had been glued with GOx on the surface of an oxygen electrode in a recently published study [51].

2.2. Treatment of GOx by nanoparticles made of Au-alloy: Multimetal NPs can combine the beneficial traits of the individual metals, for example, Ag is a good conductor while AuNPs have great biocompatibility [52]. The structure and catalytic activity of Au-Pt alloys have been extensively researched to improve the catalytic behaviour synergistically because Au has low catalytic activity in comparison to Pt [53].
For example, Kang et al. immobilised GOx on a GCE modified with AuPt nanoalloy particles/multiwall carbon NTs (MWCNTs) [54] by cross-linking with the biopolymer chitosan. Au-alloy NPs have also been utilised as GOx immobilisers and surface modifiers and to exhibit individual electrocatalytic effects. In a further work, Au and PtNPs were employed to further change the electrode's surface while CNTs with carboxylic-acid groups were covalently connected to amine residues of cysteamine that had already self-assembled on an Au electrode [55]. After immobilising GOx on the redesigned electrode, a thin layer of Nafion was added to prevent GOx loss and improve selectivity. For the creation of Ag-Au sol, sodium-bis(2-ethylhexyl)-sulfosuccinate (AOT)-cyclo-hexane reverse-micelle systems have been used [56]. The functionality of enzyme-based systems depends on the preservation of enzyme activity and integrity. The production of reverse micelles creates a hydrated shell that shields the enzyme molecules and lessens the interaction of GOx molecules with organic reagents.

2.3. Pt Nano Particles used in enzyme based glucose biosensor: Due to their antioxidant properties, PtNPs have a variety of uses in nanotechnology, catalysis, and medicine [57]. PtNPs can considerably enhance the catalytic activity used to detect glucose using hydrogen peroxide in glucose biosensors [58–59]. To increase the sensitivity of glucose biosensors, PtNPs have been combined with titania-NT arrays modified with CNTs [58], polypyrrole [59–60], ordered mesoporous carbon nanocomposite mixed with GOx [61], and iron-oxide/MWCNT/chitosan magnetic composites [62]. Pyrrole serves as a polymer backbone for the creation of stable and homogeneous cast thin films, while PtNPs provide electrical conductivity.

Additionally, polypyrrole and poly(amidoamine) dendrimers both preserve a beneficial microenvironment to safeguard GOx's bioactivity. The layer-by-layer assembled dendrimer-encapsulated PtNPs were used in a

similar manner [63]. In this study, GOx was immobilised using poly(amidoamine) dendrimers. A GOx/PtNP/functional graphene sheets/chitosan glucose biosensor was made using PtNPs as well [64]. The biosensor is highly repeatable, stable over time, and ascorbic and uric acid interference signals are negligible. Furthermore, graphene is a great contender for a sensor material due to its enormous surface area and good electrical conductivity. In a different study, negatively-charged MWCNT surfaces were adsorbed with GOx and cationic dendrimer-encapsulated PtNPs [65]. The LOD for glucose in this amperometric glucose biosensor was only 2.5 lM. The layer-by-layer method provides GOx with a safe, protected milieu and stops its leaking. In the interim, PtNPs were utilised in a self-assembling biosensor made of GOx and PtNPs encapsulated in dendrimers on nanofibrous polyaniline [66], while a different study described the usage of PtNP/mesoporous carbon matrix on a GCE using gelatin as the binder [67]. Serum sample glucose levels were satisfactorily determined using the Nafion-coated biosensor. A biosensor based on PtNPs supported on CNTs was created by Li et al. [68].

The biosensor was created using the five methods outlined below:
(1) PtNP-CNT nanocomposites were produced as a combination;
(2) Chitosan was used as a binder to cast this mixture on a GCE;
(3) Concanavalin adsorption of A onto the ready-made film;
(4) GOx was placed onto the platform; and,
(5) steps (3) and (4) were repeated to prepare multilayer films.

2.4. ZnO Nano Particles used in enzyme based glucose biosensor: ZnO nanostructures have been employed in optics, optoelectronic devices, sensors, and actuators because they have semiconducting, piezoelectric, and pyroelectric properties [69]. Additionally, ZnO nanoparticles exhibit high electrochemical activity, strong biocompatibility, chemical stability, non-toxicity, and a rapid rate of electron transfer [70]. Since GOx has an isoelectric point of 4.2 and ZnO has an isoelectric point of around 9.5, a ZnO substrate may offer a suitable surface for GOx immobilisation [71–72]. Additionally, nanostructured ZnO, like all other nanoscale materials, has a high surface-to-volume ratio, which can be credited with increasing both the surface and the GOx-loading capacity [73–74]. For instance, ZnO NPs were coated onto MWCNT-modified electrodes in a research by the Wang group to increase the stability of GOx immobilisation [75]. The GO-immobilized ZnO film was covered with a second layer of polydiallyldimethylammonium chloride to stop enzyme leakage. The created biosensing platform displayed long-term stability, greater GOx loading, reduced LOD, and improved sensitivity.

2.5. Other metals used in enzyme based glucose biosensor: Many other biosensors have exploited the general favorable properties of other MNPs. These MNPs improve the functionality and the sensitivity of enzyme-based glucose biosensors by enhancing electrocatalytic properties or by functioning as GOx immobilizer and surface modifiers. Ag has been used to increase the sensitivity of various kinds of biosensors, including glucose sensors, because it has good conductive properties [76]. In glucose biosensors, AgNPs can also serve as redox indicators [77]. The activity of free Ag+ release from AgNPs is what is being monitored in order to detect hyperglycemia utilising AgNPs. Hydrogen peroxide is created during the enzyme-substrate reaction between b-D-glucose and GOx, and it has the ability to oxidise AgNPs into free Ag+ ions.

The concentration of glucose is correlated with the number of free Ag^+ ions. Since copper is a naturally occurring cheap metal with outstanding electrochemical and catalytic properties, it has a wide range of uses, including field-emission emitters, lithium-ion electrodes, and electrical, optical, and photovoltaic devices [78–80]. A high-performance amperometric glucose biosensor was created by immobilising GOx on a CuNP/chitosan/CNT-GCE in accordance with studies on enzyme-based glucose biosensors. This sensor showed excellent selectivity, quick reaction time (less than 4 s), and good sensitivity [81]. Another biosensor

that uses CuNPs and non-conducting poly (o-aminophenol) film that has been electrochemically polymerized has been developed [82]. Palladium is one of the other metals that has been widely employed in the production of glucose sensors. The electrodeposition of poly(3,4-ethylenedioxythiophene) nanofibers was accomplished by combining an ionic liquid with a soft template (surfactant) (cosurfactant). After that, GOx was immobilised on PdNPs and PdNPs were disseminated throughout the nanofibers [83]. Li et al. used n-alkylamine-stabilized PdNPs-GOx on GCE to create a novel Pd-based biosensor.
N-alkylamines (dodecylamine and octadecyl-amine) serve as a stabilising ligand in this biosensor [84].

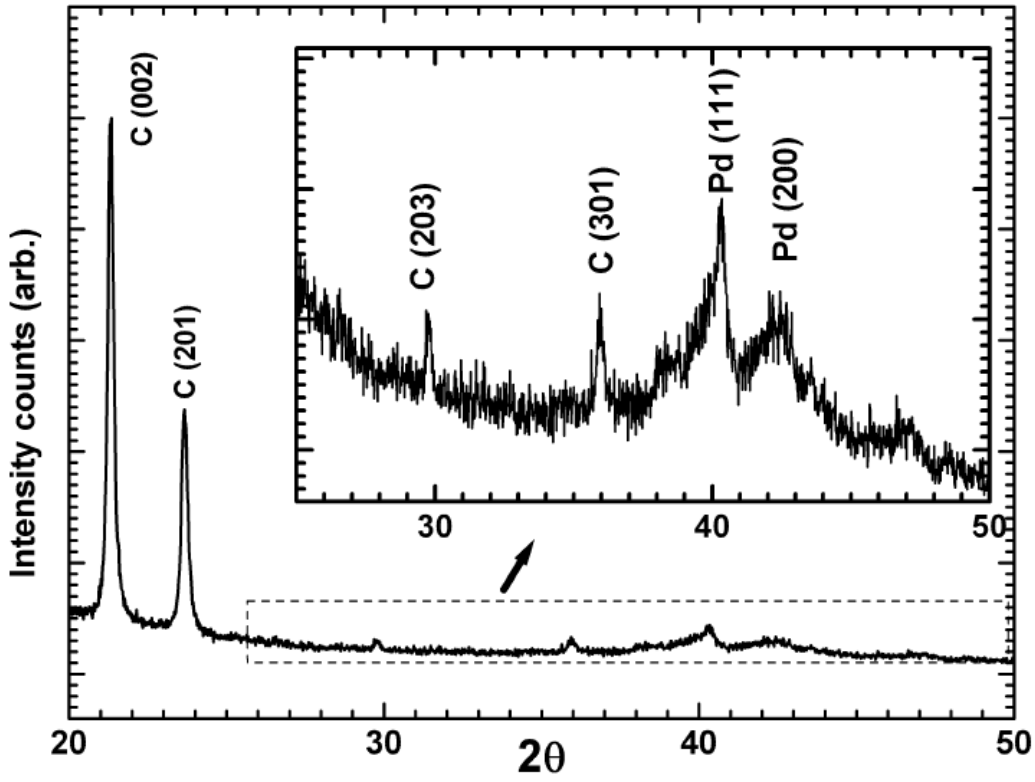

Fig 2 shows the XRD data for PdNPs-GOx on GCE to define its crystal structure. PdNPs create a novel Pd-based biosensor.

Numerous studies have discussed the use of other, less common MNPs in the manufacture of enzyme-based glucose biosensors. According to Li et al., an organic colloidal technique was used to create a biosensor based on CNT-supported PtNPs using sodium citrate as the coordination reagent and stabiliser and ethylene glycol as the reduction reagent. The biosensor was found to have a linear range of 1-23 mM and a LOD of 50 lM [85]. CNT-supported PtRuNPs were employed in a similar study [86]. AuNPs have also been added to sensitive electrochemical glucose biosensors that lack enzymes. For instance, in one study, a cysteine residue that was modified to position the protein sequence served as the direct sulfur-gold bond that fixed the periplasmic glucose receptors on AuNPs [87]. Glucose was detected on the surface of AuNPs in this investigation using periplasmic binding proteins that were genetically modified. Using these protein-AuNP complexes in biosensors to detect glucose in the micromolar range was detailed by Andreescu et al. in detail [88].

Based on a GCE modified with platinum hollow NP chains (PtHNPCs) spread atop porous AuNPs in a chitosan membrane, a novel non-enzymatic glucose sensor has been developed [89]. The GCE was initially

modified with porous AuNP-chain membranes, increasing the effective electrode surface for PtHNPC immobilisation and creating an efficient redox probe. This modified electrode demonstrated a significantly improved electrocatalytic response for glucose, with a linear response towards glucose over the concentration range of 3.0-7.7 mM and a LOD of 1.0 lM. A GCE's surface was altered using nickel hexacyanoferrate NPs created by potential cycling in a solution containing nickel (II) and hexacyano-ferrate (III) [90]. As an electrode surface modification, nickel hydroxide with graphene was used in another investigation. By increasing specific surface area and electrical conductivity, graphene is a key factor in enhancing sensor performance. This biosensor was reported to have two linear ranges, one between 1 and 10 lM, and the other between 10 and 1000 lM. LOD was determined at 0.6 lM [91].

A MWCNT-array electrode modified with cupric oxide NP was used to create a novel non-enzymatic glucose biosensor. According to reports, the system's LOD and response time are 0.2 lM and 1 s, respectively. One unique aspect of the system was the CuO/MWCNTs electrode's great resistance to chloride ion poisoning and the low interference of ascorbic acid, dopamine, and uric acid oxidation [92]. Meng and colleagues demonstrated the use of a non-enzymatic PdNP/CNT glucose biosensor in clinical samples diluted in phosphate-buffered saline (pH 7.4) by Meng and colleagues [93]. Although this work offers hope for non-enzymatic glucose sensor applications in vivo, more research is necessary before these biosensors may be used with undiluted samples. A glucose sensor based on glucose oxidation of an electrode modified with PdNP-functionalized CNTs has also been introduced by Chen et al. [94]. Additionally, PdNPs were successfully used to catalyse the oxidation of glucose, and they showed higher resistance to being poisoned by competing species (e.g., ascorbic acid, uric acid, and q-acetamidophenol). The created biosensor was used successfully to check the levels of glucose in urine samples.

3. Conclusion:

Both enzyme-based and enzyme-free glucose biosensors have benefited greatly from the design, sensitivity, and selectivity provided by nanomaterials. It has been demonstrated that different MNPs improve the effectiveness of GOx immobilisation. However, low stability results from the matching enzyme being simply denatured during the immobilisation procedure or leaching out of the films. Because enzyme-based biosensors are somewhat unstable and sensitive to changes in temperature, pH, humidity, and hazardous substances, various researchers throughout the world have been driven to hunt for enzyme-free techniques. These issues are not present in the direct electrochemical oxidation of glucose on various substrates. However, there are some drawbacks to these techniques as well (e.g., low sensitivity and poor selectivity). We point out that whereas traditional glucose biosensors currently have acceptable sensitivity, new glucose biosensors still have a long, tough way to go.

The cost of the final product should be carefully considered before including pricey nanomaterials, such as MNPs, into the construction of novel biosensors because glucose biosensors now on the market are quite inexpensive. Nobody can dispute, however, that these innovative nanosensors are more sensitive than conventional ones and that shrinking of these biosensors can lead to a wider range of applications in the future.

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